REMARKS

Applicants are in receipt of the Office Action mailed May 17, 2007, and have the following comments.

Applicants have herein amended claim 87 to refer to compositions containing a complex comprising a TC and an EEC "other than a cyclodextrin or derivative thereof"; support for this amendment can be found on e.g., page 18 at the first full paragraph. Claims 60 and 87 have been amended to clarify that the composition comprises the indicated molar ratios of EEC to TC. Finally, the molar ratio of TC to EEC of 1:1, which is disclosed in Examples 1-3 (0.131% brimonidine base (molecular weight 292.13), ion paired with 0.126% linoleic acid (molecular weight 280.44)) and is added to independent claims 60 and 87. Support for these latter amendments can be found, e.g., on page 28, Example 1.

Applicants thank the Examiner for having withdrawn the previous rejections pursuant to 35 USC §112. Applicants have carefully reviewed the newly stated grounds for rejection of the pending claims and continue to believe they are patentable in light of the cited prior art for the reasons stated in the last Reply, filed February 28, 2007, and the reasons stated below.

Rejections Pursuant to 35 USC §102

Claims 87 and 88

Claims 87 and 88 were rejected as allegedly anticipated by Desantis Jr. U.S. Patent No. 5,811,443. Applicants respectfully disagree that the claims are anticipated.

As stated by the Court of Appeals for the Federal Circuit in a recent decision, *Elan Pharmaceuticals Inc. v. Mayo Foundation*, 304 F.3d 1221, ____, 64 USPQ2d 1292, 1297 (Fed. Cir. 2002), "precedent has not improved on the words of Judge Learned Hand:

> No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier disclosure does no more than offer a starting point for further experimentation, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation.

Dewey & Almy Chemical Co. v. Mimex Co., 124 F.2d 986, 989 (2d Cir. 1942)."

Thus, anticipation under 35 USC §102 requires identity of invention. In other words, the claimed invention must be the same as that of the reference in order for the latter to anticipate the former. *Glaverbal Société Anonyme v Northlake Marketing and*

Supply, Inc., 45 F. 3d 1550, 1554, 33 U.S.P.Q. 2d 1496, 1498 (Fed. Cir. 1995). A rejection for anticipation under 35 U.S.C. §102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. *In re Spada*, 911 F. 2d 705, 708, 15 U.S.P.Q. 2d 1655, 1657 (Fed. Cir. 1990). In addition, the reference must enable the manufacture and use of the claimed invention and describe the invention sufficiently in to have placed it in possession of a person of ordinary skill in the field of the invention. *Id.*

A reference does not anticipate unless each limitation is expressly or inherently present. An inherent limitation is one that is necessarily present; invalidation based on inherency is not established by probabilities or possibilities. *See e.g., Elan Pharmaceuticals Inc. v. Mayo Foundation*, 304 F.3d 1221, ____, 64 USPQ2d 1292, 1296 (Fed. Cir. 2002).

Finally, when a claimed invention is not identically disclosed in a reference, and the rejection instead requires picking and choosing among a number of different options disclosed by the reference, then the reference does not anticipate. *Mendenhall v Astec Industries, Inc.*, 13 U.S.P.Q. 2d 1913, 1928 (E.D. Tenn. 1988) (citing *Akzo N.V.V. International Trade Commission*, 808 F.2D 1471, 1480; 1 USPQ2d 1241, 1245-46 (Fed. Cir. 1986)), affirmed, 887 F. 2d 1094, 13 U.S.P.Q. 2d 1956 (Fed. Cir. 1989).

Claim 87 is drawn to a composition comprising an ion pair complex including a therapeutic component and an efficacy enhancing

component; the complex comprises a 3:1, 2:1, 1:2 or 1:3 molar ratio of efficiency-enhancing component to therapeutic component. Further, the efficacy enhancing component is selected from the group consisting of anionic polymers, fatty acids, and mixtures thereof, and the efficient enhancing component must be present in an amount sufficient to complex substantially all of the therapeutic component in solution. Claim 88 depends from claim 87.

In the present case, the Office Action states on pages 3 and 4 that DeSantis discloses the combination of clonidine and at least one prostaglandin, as well as optional anionic mucomemetic polymers at concentrations of from 0.05% to 8.0% by weight. The Office Action identifies the prostaglandin as a "fatty acid"; the prostaglandin and anionic polymers are therefore identified as falling within the definition of efficiency enhancing components (EECs) in claims 87 and 88.

The Office Action also states on page 4 that "DeSantis discloses that the ratio of prostaglandin to clonidine is 1:1 to 1:10,000 (column 8, lines 14-17)."

Applicants first note that DeSantis does not mention, molar ratios expressly or implicitly; it refers to <u>weight</u> ratios rather than <u>molar</u> ratios. <u>This difference is a substantial one</u>; the present invention is drawn to a composition comprising ion-pair complexes of therapeutic agents and EECs in which substantially all of the therapeutic agent is in complexed form. Therefore, as a factual matter, DeSantis does not disclose molar ratios.

Nor does DeSantis disclose compositions, such as those defined by claims 87 and 88, in which substantially all the therapeutic component ("TC") is in complexed form. As explained in the present specification, the ion-pair complexes of the present invention the complexes are more able to cross lipid bilayers than a free, charged therapeutic component, thereby increasing the bioavailability of the TC. DeSantis neither expressly or implicitly discloses compositions in which the therapeutic component is substantially entirely complexed in order to optimize this advantage and to prevent or reduce possible systemic side effects caused by uncomplexed TC.

Further, the present claims are drawn to compositions in which particular molar ratios (not ranges of ratios which may include fractional ratios) of TC to EEC are present. This again is important in order to ensure that the therapeutic component is substantially entirely complexed.

The Office Action on page 4, first full paragraph, appears to argue that the molar ratio limitation of claims 87 and 88 are met by DeSantis inherently. Thus, the Office Action states therein that "depending upon the pH of the medium, ionic (EEC and TC) will combine in molar proportions so that the molar ratios recited in the claims are inherent to specific [TC-EEC] pair." Applicants respectfully submit that a careful review of the claim language of claims 87 and 88 will reveal that this is not true.

As stated above, claims 87 and 88 require that substantially all the therapeutic component is complexed with EEC. There is no disclosure that the compositions disclosed by DeSantis 1) contain ion pairs at all, 2) contain complexes at all, c) limit the ratio of TC to EEC to prevent substantial free TC to exist in solution, or d) provide a 3:1, 2:1, 1:2 or 1:3 molar ratio of EEC to TC. The compositions of DeSantis may contain gelling polysaccharides, which may be uncharged, rather than anionic polymers.

Also as stated above, an inherent limitation is one that is necessarily present in the prior art; invalidation based on inherency is not established by probabilities or possibilities. *See e.g., Elan Pharmaceuticals Inc. v. Mayo Foundation*, 304 F.3d 1221, ____, 64 USPQ2d 1292, 1296 (Fed. Cir. 2002). In the present case, no example is provided in DeSantis in which a 3:1, 2:1, 1:2 or 1:3 molar ratio of EEC to TC is described, and it is probable that a combination of a TC at the higher value given for clonidine (2% by weight; see column 8, lines 6, and an EEC at, for example, the lower concentration given for a prostaglandin (0.0001%; see column 8, line 13) would meet neither the ratio limitations nor the requirements that "substantially all" of the TC be complexed of claims 87 and 88. Furthermore, the pH of the compositions of DeSantis may be as low as 3.5, at which pH many anionic polymers are not charged. Thus, in neither case are the limitations of the claims "necessarily present" in the disclosure of DeSantis, and the limitations are therefore not inherent in the disclosure of DeSantis.

Finally, the Office Action refers the formation of a complex between the clonidine derivative (which may or may not be charged) and the polymers of DeSantis as "plausible". However, conjecture as to plausibility is insufficient to establish an inherent disclosure; invalidation based on inherency is not established by probabilities or possibilities. *See e.g., Elan Pharmaceuticals Inc. v. Mayo Foundation*, 304 F.3d 1221, ____, 64 USPQ2d 1292, 1296 (Fed. Cir. 2002).

In sum, Applicants respectfully submit that there is no disclosure of the presently claimed compositions in DeSantis, and therefore DeSantis neither inherently or expressly anticipates the invention of claims 87 and 88.

Claims 87, 88 and 90

Claims 87, 88 and 90 have been rejected as allegedly anticipated by Beck et al., US6358935. Applicants respectfully traverse this rejection for the following reasons.

The May 17, 2007 Office Action characterizes Beck as disclosing a composition comprising 0.2% brimonidine, 0.5% carboxymethylcellulose and cyclodextrin in Example 2. The Office Action states that Beck discloses the formation of a complex between cyclodextrin and brimonidine and that it envisions a molar ratio of cyclodextrin to active agent in the range of 10:1 to about 1:1, and "points within this disclosed range touch the recited ratio" of the present claims. *See* Office Action at page 5, Section

3. This is factually inaccurate.

Applicants have herein amended claim 87 to refer to compositions containing a complex comprising a TC and an EEC "other than a cyclodextrin or derivative thereof"; thus the Office Action's arguments concerning anticipation based upon a cyclodextrin EEC is now moot.

With respect to the Office Action's arguments that the possible combination of brimonidine and carboxymethylcellulose ("CMC") disclosed by Beck anticipates claims 87, 88 and 90, Applicants respectfully disagree. As discussed above, claim 87, the sole independent claim of this group, requires that the compositions described therein provide a 3:1, 2:1, 1:2 or 1:3 molar ratio of EEC to TC and that substantially all the TC be complexed with EEC.

Nor are these limitations or features of the invention inherent in the disclosure of Beck, whose examples disclose a concentration for brimonidine of 0.2% and a concentration of CMC of 0.5%, both by weight; the weight ratio of brimonidine to CMC in these examples is therefore 1 to 2.5. However the comparison of this weight ratio to the claimed molar ratio is a comparison of apples to oranges.

There is absolutely no disclosure in Beck of the molecular weight of the CMC to be used, so there is no express or inherent disclosure of the molar ratios of CMC to brimonidine used in the

Examples of Beck. For illustrative purposes only, however (and not as an admission), usually the molecular weight of CMC is at least about 50 KDa and may be as much as several million Daltons (*see e.g.*, DeSantis et al. US Patent 5,811,443, column 8, liners 49-51). The molecular weight of brimonidine base is 292.135 Da.

Thus, 0.2%(w/v) of brimonidine base (the charged species) equals 0.2g/100 ml, or 0.2g/292.13 = 6.8×10^{-4} moles brimonidine per 100 ml. And 0.5%(w/v) of CMC having a molecular weight of, for example, 50,000 Daltons equals 0.5g CMC/100 ml or 0.5/50,000 = 1×10^{-5} moles CMC per 100 ml. Therefore, 0.2% brimonidine tartrate in the same solution with 0.5% $CMC_{(MW\ 50\ KDa)}$ yields a $(6.8 \times 10^{-4})/(1 \times 10^{-5})$ or 68:1 molar ratio of brimonidine to CMC; this ratio would only increase if the MW of the CMC were larger. Given that claims 87, 88 and 90 require a molar ratio of 3:1, 2:1, 1:2 or 1:3 TC to EEC, it is clear that Beck cannot anticipate these claims since it does not in any way disclose these required molar ratios.

Claims 60-62, 64, 68, 87, and 88

Claims 60-62, 64, 68, 87, and 88 were rejected as anticipated pursuant to 35 USC §102(b), or in the alternative, made obvious under 35 USC §103(a) by Uehara et al., JP 11-130656. Applicants respectfully traverse this rejection for the reasons set forth below.

Uehara discloses a ω-3-based polyunsaturated fatty acid or its derivative at 0.0001% to 10% by weight (preferably 0.01% to 5% by

weight) and preferably at east one agent selected from the group consisting of a phosphodiesterase inhibitor, cyclic AMP (cAMP) or a plant extract containing cAMP, β-adrenergic stimulant or an α-2 adrenergic inhibitor, an stringent, a blood circulation accelerant, and a lipase activity accelerant. *See* Uehara, Abstract.

As above, the independent claims 60 and 87, require that the compositions described therein provide a 3:1, 2:1, 1:2 or 1:3 molar ratio of EEC to TC, and that substantially all the TC be complexed with EEC. As in Beck, Uehara never discusses molar ratios, and does not provide any disclosure of a composition in which the molar ratios of TC to EEC are (or should be) 3:1, 2:1, 1:2 or 1:3. Furthermore, Uehara never discloses that the EEC component in its compositions, be present in an amount sufficient to complex substantially all the therapeutic component in solution. Indeed, the abstract of Uehara states that a "therapeutic agent" is not inherently present but is only "preferably" present.

For all these reasons Uehara cannot anticipate present claims 60 and 87 or their dependent claims.

With regard to obviousness, The Examiner states on page 6 of the Office Action that because 1 mole of Ca^{++} combines with 1 mole of SO_4^- under suitable conditions, "it flows" that ionic efficiency enhancing composition and ionic therapeutic component will combine in molar proportions to form ion pairs. Actually this is only true if the ionic EEC and TC are of opposing charge; and Uehara does not disclose ion pairing or combining TCs with charges opposite to

those of any fatty acid.

However, the claims have been amended to clarify that the composition comprises TC to EEC at a molar ratio of 3:1, 2:1, 1:2 or 1:3. Thus, as claimed the composition contains TC that is substantially completely in complex, and EEC at a given molar ratio to the EEC. Thus, even accepting *arguendo* the Examiner's conjecture that complexes would form at a given ratio, there is no disclosure supporting the conclusion that a person of ordinary skill in the art should combine EEC and TC at these ratios, at a concentration of EEC sufficient to complex substantially all the TC. Nor has the Examiner provided any reasoning to indicate why this would be the case. Only the present application provides this invention, and lacking knowledge of the instant invention, nothing in Uehara would provide any incentive for a person to devise the present invention.

Claim 89 was rejected as allegedly obvious over Beck et al. US 6358935. Applicants traverse this rejection.

As stated above, Beck does not anticipate the present invention. The Examiner alleges that Beck does not disclose the quinoxaline of claim 89, but it would have been obvious to a person of ordinary skill in the art (POSA) to make the present invention by following the teaching of Beck where the composition contains methylcellulose and/or cyclodextrin and to substitute 2-imidazolin-2-ylamino) quinoxaline for brimonidine tartrate with the expectation that the composition would produce the same effect in

the eye.

Claim 89 requires that the composition contain TC and EEC at a molar ratio of 3:1, 2:1, 1:2 or 1:3, and that the EEC be present in an amount sufficient to complex substantially all of the TC. Applicants point out that brimonidine tartrate, as disclosed in Beck, would not form the claimed ion pair, because brimonidine muyst be in its charged (Base) form to for an ion complex. There is no such disclosure in Beck, nor has the Examiner pointed to any teaching in Beck that would lead to such a composition, nor indeed even any "problem" disclosed in Beck or generally known to those of skill in the art for which the present invention provides a "solution". Thus, the POSA, following the teaching of Beck, would not be led to the following compositions, regardless of the nature of the quinoxaline. The fact that Beck does not contemplate the compound claimed in claim 89 is only one more reason why Beck does not render the invention of claim 89 obvious.

Applicants also remind the Examiner of the results of Table 1 of the specification, which show the unexpected improvement in sedation scores, particularly 2, 3, and 4 hours after topical application, in animals given 0.2% brimonidine tartrate versus 0.2% brimonidine (base) in an 1:1 molar ratio ion pair complex with a fatty acid, linoelic acid (0.131 brimonidine base and 0.126% linoelic acid; see page 28, Example 1)). Thus even if a *prima facie* case of obviousness were established (which Applicants vehemently deny) these unexpected results show that the ion pair compositions of the present invention provide benefits that could

not have been predicted based on Beck et al.

Claims 60-63, 65, 66, 68, 72, 73, 77, and 87-90 were rejected as allegedly obvious over Gil, et al., US 6294553. Gil is alleged to disclose a composition comprising brimonidine tartrate plus oleic acid or anionic surfactant or polymers. Again, the Examiner alleges, this time on page 8 of the Office Action, that because 1 mole of Ca^{++} combines with 1 mole of SO_4^- under suitable conditions, "it flows" that ionic efficiency enhancing composition and ionic therapeutic component will combine in molar proportions to form ion pairs. The Examiner alleges there is no evidence that the cited ratios provide any unexpected results.

As with Beck, Gil does not disclose the formation of ion pairs of brimonidine base with an EEC, or compositions comprising a TC and an EEC at a molar ratio of 3:1, 2:1, 1:2 or 1:3 in which substantially all the therapeutic component is complexed with the EEC. Gil does not suggest any problem that might be solved by the compositions of the present invention.

Additionally, as with Beck, the Examiner has not pointed to any teaching in Gil that would lead to the compositions of the challenged claims, nor indeed even any "problem" disclosed in Beck or generally known to those of skill in the art for which the present invention provides a "solution". Thus, the POSA, following the teaching of Beck, would not be led to the following compositions.

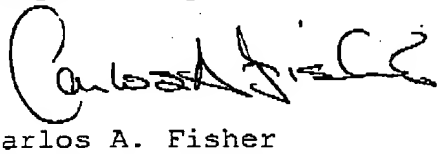
Finally, the results of Table 1 of the specification, demonstrate the unexpected improvement in sedation scores, particularly 2, 3, and 4 hours after topical application, in animals given 0.2% brimonidine in an 1:1 molar ratio ion pair complex with a fatty acid, linoelic acid (0.131 brimonidine and 0.126% linoelic acid; see page 28, Example 1)) as opposed to 0.2% brimonidine tartrate. These unexpected results show that the claimed compositions provide benefits that could not have been predicted based on Gil et al.

CONCLUSION

For the foregoing reasons the claims are thought to be in condition for allowance, and the Applicants respectfully request that the Examiner issue a Notice to that effect. If the Examiner has any questions or comments, a telephone call to the undersigned is respectfully solicited.

This Reply is being filed benfore expiration of the three month shortened statutory period, therefore no fee is thought to be due in connection with this communication. However, if Applicants are in error in this regard, kindly use Deposit Account 01-0885 for the payment of any additional charge now due.

Respectfully submitted,



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